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Copy for the Elected Office (EO/US) 1653 PC

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

TECH CENTER 1600

To:

PLOUGHMANN, VINGTOFT & PARTNERS A/S
Sankt Annæ Plads 11
P.O. Box 3007
DK-1021 Copenhagen K
DANEMARK

Date of mailing (day/month/year) 15 May 2000 (15.05.00)	
Applicant's or agent's file reference 20479 PC 1	**IMPORTANT NOTIFICATION**
International application No. PCT/DK99/00118	**International filing date** (day/month/year) 09 March 1999 (09.03.99)

1. The following indications appeared on record concerning:

☐ the applicant ☐ the inventor ☒ the agent ☐ the common representative

Name and Address	State of Nationality	State of Residence
PLOUGHMANN, VINGTOFT & PARTNERS A/S Sankt Annæ Plads 11 P.O. Box 3007 DK-1021 Copenhagen K Denmark	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address	State of Nationality	State of Residence
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:
No longer agent in this application
any further correspondence should be sent to the applicant.

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☒ the International Preliminary Examining Authority
☐ the designated Offices concerned
☒ the elected Offices concerned
☐ other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Marie-José Devillard
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994)

003285278

PATENT COOPERATION TREATY

09/341590

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 18 November 1999 (18.11.99)	
International application No. PCT/DK99/00118	**Applicant's or agent's file reference** 20479 PC 1
International filing date (day/month/year) 09 March 1999 (09.03.99)	**Priority date** (day/month/year) 09 March 1998 (09.03.98)
Applicant LARSEN, Bjarne, Due	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

08 October 1999 (08.10.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer F. Baechler
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

QC 16M2
09/342,915-90

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

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Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
20479 PC 1		

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/DK99/00118	09/03/1999	09/03/1998

International Patent Classification (IPC) or national classification and IPC
C07K1/107

Applicant
ZEALAND PHARMACEUTICALS A/S et al.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which hav been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 10 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☒ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
08/10/1999	11.07.2000

Name and mailing address of the international preliminary examining authority:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
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Authorized officer

G. Willière

Telephone No. +49 89 2399 8548

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/DK99/00118

I. Basis f th r port

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-19,21-84	as originally filed	
20	with telefax of	27/03/2000

Claims, No.:

1-49	with telefax of	27/03/2000

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

   ☐ copy of the earlier application whose priority has been claimed.

   ☐ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

see separate sheet

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 1-49
	No:	Claims
Inventive step (IS)	Yes:	Claims 1-49
	No:	Claims
Industrial applicability (IA)	Yes:	Claims 1-49
	No:	Claims

2. Citations and explanations

see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item II
Priority

The subject-matter of the amended version of the claims is believed to substantially being entitled to the claimed priority. It has to be emphasised the at least the corresponding disclosure of D1 and D2 is entitled to said priority. This is why D1 and D2 are not comprised within the prior art according to Rule 64.1 PCT.

Re Item V
Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The presently claimed subject-matter is believed to be both novel and to involve an inventive step since none of the documents D3 to D5 disclose or suggest the stabilising effect towards proteolytic cleavage of the stabilising peptides sequences of the presently claimed subject-matter covalently linked via a peptidic bond to the core peptide in combination with the pharmacological properties of said core peptide not being affected (article 33(2) and (3) PCT).

Re Item VI
Certain documents cited

Certain published documents (Rule 70.10)

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO 98/11126	19.03.1998	09.09.1997	09.09.1996
WO 98/22577	28.05.1998	17.11.1997	15.11.1996
			25.06.1997

Re Item VIII
Certain observations on the international application

1. The subject-matter of claim 1 needs clarification by deletion of the comma after

the expression "peptide sequence" in line 6 (Article 6 PCT).

2. The wording used in claim 8 "at least **two** Lys amino acid units, such as at least **three** Lys amino acid units" is not clear. The wording "at least" preceding "three Lys amino acid units" should be deleted (Article 6 PCT).

3. The restriction (in case it should be one) "or when said pharmacologically active peptide X is not orally absorbed, said conjugate is absorbed" (see claim 1) should be clarified, i.e. it is doubted whether this feature represents a functional restriction to the compound claim or not; moreover it is not clear what is meant by oral absorption, or what is meant by a compound not being orally absorbed . Moreover it should be clarified whether this restriction applies to all the compounds as claimed (Article 6 PCT).

4. Claim 23 referring to peptide conjugates of lines 15 to 17 and 19 to 21. These lines cite four different peptides, wherein two of them do not represent peptide conjugates. Shouldn't these sequences be linked together between the residues Ser and Arg (Article 6 PCT)?

5. It should also be notice that the compound H-Tyr-Gly-Gly-Phe-Leu-Lys_6-OH which is disclaimed in claim 1 is still claimed in claim 23 being dependent from said claim 1 (Article 6 PCT).

H-Ser-Val-Ser-Glu-Ile-Gln-Leu-Met-His-Asn-Leu-Gly-Lys-His-Leu-Asn-Ser-Met-Glu-Arg-Val-Glu-Trp-Leu-Arg-Lys-Lys-Leu-Gln-Asp-Val-His-Asn-Phe-Lys_6-OH (PTH(1-34)(Human)-Lys_6-OH);

H-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Lys_6-OH (GLP-1-(7-36)(Human)-Lys_6-OH);

H-Gly-Gly-Thr-Tyr-Ser-Cys(Acm)-His-Phe-Gly-Pro-Leu-Thr-Trp-Val-Cys(Acm)-Lys-Pro-Gln-Gly-Gly-Lys_6-OH (EMP-1-Lys_6-OH);

H- Lys_6-Gly-Gly-Thr-Tyr-Ser-Cys(Acm)-His-Phe-Gly-Pro-Leu-Thr-Trp-Val-Cys(Acm)-Lys-Pro-Gln-Gly-Gly-OH (Lys_6-EMP-1-OH);

H- Lys_6-Gly-Gly-Thr-Tyr-Ser-Cys(Acm)-His-Phe-Gly-Pro-Leu-Thr-Trp-Val-Cys(Acm)-Lys-Pro-Gln-Gly-Gly- Lys_6-OH (Lys_6-EMP-1- Lys_6-OH);

H-Aib-His-2-D-Nal-D-Phe-Lys-$(Lys)_6$-NH_2 (GHRP-$(Lys)_6$-NH_2);

H-Tyr-Gly-Gly-Phe-Leu-Lys-Lys-Glu-Glu-Glu-Lys--OH (Leu-enkephalin-Lys-Lys-Glu-Glu-Glu-Lys-OH);

H-Tyr-Gly-Gly-Phe-Leu-Lys-Glu-Glu-Glu-Glu-Lys--OH (Leu-enkephalin-Lys-Glu-Glu-Glu-Glu-Lys-OH);

H-Tyr-Gly-Gly-Phe-Leu-Lys-Glu-Glu-Glu-Glu-Lys--OH (Leu-enkephalin-(Lys-Glu_4-Lys);

H-Tyr-Gly-Gly-Phe-Leu-(Dpr)$_6$-OH (Leu-enkephalin-(Dpr)$_6$-OH)

H-Lys_6-Tyr-Gly-Gly-Phe-Leu-OH (H-Lys_6-Leu-enkephalin);

CLAIMS:

1. A pharmacologically active peptide conjugate having a reduced tendency towards enzymatic cleavage comprising X and Z,

wherein X is a pharmacologically active peptide sequence, and

wherein Z is a stabilising peptide sequence, of 4-20 amino acid units covalently bound to X via a peptide bond wherein each amino acid unit in said stabilising peptide sequence Z is selected from the group consisting of Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Orn, 2,4-diaminobutanoic acid (Dbu), 2,3-diaminopropanoic acid (Dpr) and Met, and

wherein the ratio between the half-life of said peptide conjugate and the half-life of the corresponding pharmacologically active peptide sequence, X, when treated with carboxypeptidase A or leucine aminopeptidase in about 50 mM phosphate buffer solution at about pH 7.4 at about 37°C or in serum or plasma is at least about 2, preferably at least about 3, such as at least about 5, more preferably at least about 7, such as at least about 9, e.g. at least about 10, or when said pharmacologically active peptide X is not orally absorbed, said conjugate is absorbed, or a salt thereof,
with the proviso that said pharmacologically active peptide conjugate is not selected from
H-Trp-Ala-Gly-Gly-Asp-Ala-Ser-Gly-Glu-(Lys-Glu)$_2$-OH,
H-Trp-Ala-Gly-Gly-Asp-Ala-Ser-Gly-Glu-(Glu)$_6$-OH,
H-Tyr-Gly-Gly-Phe-Leu-(Glu)$_6$-OH and
H-Tyr-Gly-Gly-Phe-Leu-(Lys)$_6$-OH.

2. A peptide conjugate according to claim 1, wherein Z is covalently bound to X at the C-terminal carbonyl function of X.

3. A peptide conjugate according to claim 1, wherein Z is covalently bound to the N-terminal nitrogen atom of X.

4. A peptide conjugate according to claim 1, wherein a first sequence (Z) is covalently bound to X at the C-terminal carbonyl function of X and a second sequence (Z) is covalently bound to the N-terminal nitrogen atom of X.

5. A peptide conjugate according to claim 1, wherein Z is covalently bound to a nitrogen atom on the side chain of a lysine, arginine or histidine residue or a carbonyl function on the side chain of glutamic acid or aspartic acid of X.

6. A peptide conjugate according to any of the preceding claims, wherein Z consists of 4-15, preferably 4-10, more preferably 4-7, such as 6 amino acid units.

7. A peptide conjugate according to claim 6, wherein each amino acid unit in Z is selected from the group consisting of Glu, Lys and Met.

8. A peptide conjugate according to any of claims 6 or 7, wherein Z comprises at least one Lys amino acid unit, preferably at least two Lys amino acid units, such as at least three Lys amino acid units, e.g. at least four Lys amino acid units, more preferably at least five Lys amino acid units, such as six Lys amino acid units.

9. A peptide conjugate according to claim 8, wherein Z is $(Lys)_n$, wherein n is an integer in the range from 4 to 15, preferably in the range from 4 to 10, such as in the range from 4 to 8, e.g. in the range from 4 to 6.

10. A peptide conjugate according to claim 9, wherein Z is Lys_4, Lys_5 or Lys_6.

11. A peptide conjugate according to claim 10, wherein Z is Lys_6.

12. A peptide conjugate according to claim 6, wherein Z is $(Lys\text{-}Xaa)_m$ or $(Xaa\text{-}Lys)_m$, wherein m is an integer in the range from 2 to 7, and each Xaa is independently selected from the group consisting of Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Arg, His, Orn, 2,4-diaminobutanoic acid, 2,3-diaminopropanoic acid and Met.

13. A peptide conjugate according to claim 12, wherein Z is $(Lys\text{-}Xaa)_3$ or $(Xaa\text{-}Lys)_3$, wherein each Xaa is independently selected from the group consisting of Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Arg, His, Orn, 2,4-diaminobutanoic acid, 2,3-diaminopropanoic acid and Met.

14. A peptide conjugate according to claim 13, wherein Z is $(Lys\text{-}Glu)_3$ or $(Glu\text{-}Lys)_3$.

15. A peptide conjugate according to any of claims 6 or 8, wherein Z is $Lys_p\text{-}Xaa_q$ or $Xaa_p\text{-}Lys_q$, wherein p and q are integers in the range from 1 to 14, with the proviso that p+q is in the range of 3-15, and each Xaa is independently selected from the group consisting of Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Arg, His, Orn, 2,4-diaminobutanoic acid, 2,3-diaminopropanoic acid and Met.

16. A peptide conjugate according to claim 15, wherein Z is $Lys_3\text{-}Xaa_3$ or $Xaa_3\text{-}Lys_3$, wherein each Xaa is independently selected from the group consisting of Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Arg, His, Orn, 2,4-diaminobutanoic acid, 2,3-diaminopropanoic acid and Met.

17. A peptide conjugate according to claim 16, wherein Z is $Lys_3\text{-}Glu_3$ or $Glu_3\text{-}Lys_3$.

18. A peptide conjugate according to any of claims 1 to 17, wherein Z consists of L-amino acids only.

19. A peptide conjugate according to any of claims 1-6, wherein Z is $(Dbu)_n$ or $(Dpr)_n$, wherein n is an integer in the range from 4 to 15, preferably in the range from 4 to 10, such as in the range from 4 to 8, e.g. in the range from 4 to 6.

20. A peptide conjugate according to claim 19, wherein Z is Dpr_6.

21. A peptide conjugate according to any of the preceding claims, wherein said pharmacologically active peptide sequence (X) consists of at the most 75 amino acid units, such as at the most 65, e.g. a the most 60, preferably at the most 55, such as at the most 53, e.g. at the most 50.

22. The peptide conjugate according to claim 21, wherein X is selected from the group consisting of enkephalin, Leu-enkephalin, Met-enkephalin, angiotensin I, angiotensin II, vasopressin, endothelin, vasoactive intestinal peptide, neurotensin, endorphins, insulin, gramicidin, paracelsin, delta-sleep inducing peptide, gonadotropin-Releasing hormone, human parathyroid hormone (1-34), truncated erythropoietin analogues, specifically EMP-1, Atrial natriuretic peptide (ANP, ANF), human brain natriuretic peptide (hBNP), cecropin, kinetensin, neurophysins, elafin, guamerin, atriopeptin I, atriopeptin II, atriopeptin III, deltorphin I, deltorphin II, vasotocin, bradykinin, dynorphin, dynorphin A, dynorphin B, growth hormone release factor, growth hormone, growth hormone releasing peptide, oxytocin, calcitonin, calcitonin gene-related peptide, calcitonin gene-related peptide II, growth hormone releasing peptide, tachykinin, adrenocorticotropic hormone (ACTH), brain natriuretic polypeptide, cholecystokinin, corticotropin releasing factor, diazepam binding inhibitor fragment, FMRF-amide, galanin, gastric releasing polypeptide, gastric inhibitory polypeptide, gastrin, gastrin releasing peptide, glucagon, glucagon-like peptide-1, glucagon-like peptide-2, LHRH, melanin concentrating hormone, melanocyte stimulating hormone (MSH), alpha-MSH, morphine modulating peptides, motilin, neurokinin A, neurokinin B, neuromedin B, neuromedin C, neuromedin K, neuromedin N, neuromedin U, neuropeptide K, neuropeptide Y, pituitary adenylate cyclase activating polypeptide (PACAP), pancreatic polypeptide, peptide YY, peptide histidine-methionine amide (PHM), secretin, somatostatin, substance K, thyrotropin-releasing hormone (TRH), kyotorphin, melanostatin (MIF-1), thrombopoeitin analogs, in particular AF 12505 (Ile-Glu-Gly-Pro-Thr-Leu-Arg-Gln-Trp-Leu-Ala-Ala-Arg-Ala), insulin-like growth factor I (57-70) (Ala-Leu-Leu-Glu-Thr-Tyr-Cys-Ala-Thr-Pro-Ala-Lys-Ser-Glu), insulin-like growth factor I (30-41) (Gly-Tyr-Gly-Ser-Ser-Ser-Arg-Arg-Ala-Pro-Gln-Thr), insulin-like growth factor I (24-41)(Tyr-Phe-Asn-Lys-Pro-Thr-Gly-Tyr-Gly-Ser-Ser-Ser-Arg-Arg-Ala-Pro-Gln-Thr), insulin-like growth factor II (33-40) (Ser-Arg-Val-Ser-Arg-Arg-Ser-Arg), insulin-like growth [tyro] factor II (33-40) (Tyr-Ser-Arg-Val-Ser-Arg-Arg-Ser-Arg), insulin-like growth factor II (69-84) (Asp-Val-Ser-Thr-Pro-Pro-Thr-Val-Leu-Pro-Asp-Asn-Phe-Pro- Arg-Tyr), growth hormone (GH)-releasing peptide-6 (GHRP-6) (His-DTrp-Ala-Trp-DPhe-Lys-NH2), beta-Interleukin I (163-171) (Val-Gln-Gly-Glu-Glu-Ser-Asn-Asp-Lys), beta-Interleukin II (44-56) (Ile-Leu-Asn-Gly-Ile-Asn-Asn-Tyr-Lys-Asn-Pro-Lys-Leu), Interleukin II (60-70) (Leu-Thr-Phe-Lys-Phe-Tyr-Met-Pro-Lys-Lys-Ala), exendin-4 (GLP-1 analog) (His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Glu-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2), exendin-3 (GLP-1 analog) (His-Ser-Asp-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser), [Cys(Acm)20,31] epidermal growth factor (20-31) Cys(Acm)-Met-His-Ile-Glu-Ser-Leu-Asp-Ser-Tyr-Thr-Cys(Acm), bivalirudin (Hirul g) (D-Phe-Pro-Arg-Pro-(Gly)4-Asn-Gly-Asp-Phe-Glu-Glu-Ile-Pro-Glu-Glu-Tyr-Leu), hirulog-1 D-Phe-Pro-Arg-Pro-(Gly)4-Asn-Gly-Asp-Phe-Glu-Glu-Ile-Pro-Glu-Tyr-Leu, C-type natriuretic peptide (1-53) (CNP) (Asp-Leu-Arg-Val-Asp-Thr-Lys-Ser-Arg-Ala-Ala-Trp-Ala-Arg-Leu-Leu-Gln-Glu-His-Pro-Asn-Ala-Arg-Lys-Tyr-Lys-Gly-Ala-Asn-Lys-Lys-Gly-Leu-Ser-Lys-Gly-Cys-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile-Gly-Ser-Met-Ser-Gly-Leu-Gly-Cys; Disulfide bridge: Cys37-Cys53), "Mini ANP" (Met-Cys-His-cyclohexylAla-

Gly-Gly-Arg-Met-Asp-Arg-Ile-Ser-Cys-Tyr-Arg, disulfide bridge cys2-cys13), Melanotan-II (also known as MT-II, alpha-MSH4-10-NH2, or Ac-Nle4-Asp5-His6-D-Phe7-Arg8-Trp9-Lys10), thymosin alpha1 (TA1) (Ac-Ser-Asp-Ala-Ala-Val-Asp-Thr-Ser-Ser-Glu-Ile-Thr-Thr-Lys-Asp-Leu-Lys-Glu-Lys-Lys-Glu-Val-Val-Glu-Glu-Ala-Glu-Asn), ornipressin (also known as 8-ornithine-vasopressin, (POR-8), [Phe2,Ile3,Orn8]vasopressin), Cys-Phe-Ile-Gln-Asn-Cys-Pro-Orn-Gly-NH2, Disulfide bridge: Cys1-Cys6), octreotide (201-995) (DPhe-Cys-Phe-DTrp-Lys-Thr-Cys-Thr-ol; disulfide bridge: Cys2-Cys7), eptifibatide (INTEGRILIN), calcitonin gene-related peptide (CGRP) (Ala-Cys-Asp-Thr-Ala-Thr-Cys-Val-Thr-His-Arg-Leu-Ala-Gly-Leu-Leu-Ser-Arg-Ser-Gly-Gly-Val-Val-Lys-Asn-Asn-Phe-Val-Pro-Thr-Asn-Val-Gly-Ser-Lys-Ala-Phe-NH_2; Disulfide bridge: Cys2-Cys7), endomorphin-1 Tyr-Pro-Trp-Phe-NH2; endomorphin-2 Tyr-Pro-Phe-Phe-NH_2, nociceptin (also known as Orphanin FQ, Phe-Gly-Gly-Phe-Thr-Gly-Ala-Arg-Lys-Ser-Ala-Arg-Lys-Leu-Ala-Asn-Gln), angiotensinogen (1-13) (Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu-Val-Ile-His), adrenomodullin (1-12) (Tyr-Arg-Gln-Ser-Met-Asn-Asn-Phe-Gln-Gly-Leu-Arg), antiarrhytmic peptide (AAP) (Gly-Pro-Hyp-Gly-Ala-Gly), Antagonist G (Arg-DTrp-(nMe)Phe-DTrp-Leu-Met-NH_2), indolicidin (Ile-Leu-Pro-Trp-Lys-Trp-Pro-Trp-Trp-Pro-Trp-Arg-Arg-NH_2), osteocalcin (37-49) (Gly-Phe-Gln-Glu-Ala-Tyr-Arg-Arg-Phe-Tyr-Gly-Pro-Val), cortistatin 29 (1-13) (Glp)-Glu-Arg-Pro-Pro-Leu-Gln-Gln-Pro-Pro-His-Arg-Asp), cortistatin 14 Pro-Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Ser-Ser-Cys-Lys; Disulfide bridge: Cys2-Cys13, PD-145065 (Ac-D-Bhg-Leu-Asp-Ile-Ile-Trp), PD-142893 (Ac-D-Dip-Leu-Asp-Ile-Ile-Trp), fibrinogen binding inhibitor peptide (His-His-Leu-Gly-Gly-Ala-Lys-Gln-Ala-Gly-Asp-Val), leptin (93-105) (Asn-Val-Ile-Gln-Ile-Ser-Asn-Asp-Leu-Glu-Asn-Leu-Arg), GR 83074 (Boc-Arg-Ala-DTrp-Phe-DPro-Pro-Nle-NH_2), Tyr-W-MIF-1 (Tyr-Pro-Trp-Gly-NH_2), parathyroid hormone related peptide (107-111) (Thr-Arg-Ser-Ala-Trp), angiotensinogen (1-14) Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu-Val-Ile-His-Asn, Leupeptin (Ac-Leu-Leu-Arg-CHO), and any modified or truncated analogue thereof.

23. A peptide conjugate according to any of the previous claims wherein the conjugate is

H-Tyr-Ala-Asp-Ala-Ile-Phe-Thr-Asn-Ser-Tyr-Arg-Lys-Val-Leu-Gly-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Met-Ser Arg-Gln-Gln-Gly-Glu-Ser-Asn-Gln-Glu-Arg-Gly-Ala-Arg-Ala-Arg-Leu-Lys_6-NH_2 (GHRH(1-44)(Human)-Lys_6-NH_2);

H-Tyr-Ala-Asp-Ala-Ile-Phe-Thr-Asn-Ser-Tyr-Arg-Lys-Val-Leu-Gly-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Met-Ser Arg-Gln-Gln-Gly-Glu-Ser-Asn-Gln-Glu-Arg-Gly-Ala-Arg-Ala-Arg-Leu-Glu_6-NH_2 (GHRH (1-44)(Human)-Glu_6-NH_2);

H- Lys_6-Ser-Val-Ser-Glu-Ile-Gln-Leu-Met-His-Asn-Leu-Gly-Lys-His-Leu-Asn-Ser-Met-Glu-Arg-Val-Glu-Trp-Leu-Arg-Lys-Lys-Leu-Gln-Asp-Val-His-Asn-Phe-OH (Lys_6-PTH(1-34)(Human)-OH);

H-Ser-Val-Ser-Glu-Ile-Gln-Leu-Met-His-Asn-Leu-Gly-Lys-His-Leu-Asn-Ser-Met-Glu-Arg-Val-Glu-Trp-Leu-Arg-Lys-Lys-Leu-Gln-Asp-Val-His-Asn-Phe-Lys_6-OH (PTH(1-34)(Human)-Lys_6-OH);

H-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Lys_6-OH (GLP-1-(7-36)(Human)-Lys_6-OH);

H-Gly-Gly-Thr-Tyr-Ser-Cys(Acm)-His-Phe-Gly-Pro-Leu-Thr-Trp-Val-Cys(Acm)-Lys-Pro-Gln-Gly-Gly-Lys$_6$-OH (EMP-1-Lys$_6$-OH)

H- Lys$_6$-Gly-Gly-Thr-Tyr-Ser-Cys(Acm)-His-Phe-Gly-Pro-Leu-Thr-Trp-Val-Cys(Acm)-Lys-Pro-Gln-Gly-Gly-OH (Lys$_6$-EMP-1-OH)

H- Lys$_6$-Gly-Gly-Thr-Tyr-Ser-Cys(Acm)-His-Phe-Gly-Pro-Leu-Thr-Trp-Val-Cys(Acm)-Lys-Pro-Gln-Gly-Gly-Lys$_6$-OH (Lys$_6$-EMP-1-Lys$_6$-OH) :

H-Aib-His-2-D-Nal-D-Phe-Lys-(Lys)$_6$-NH_2 (GHRP-(Lys)$_6$-NH_2);

H-Tyr-Gly-Gly-Phe-Leu-Lys-Lys-Glu-Glu-Glu-Lys--OH (Leu-enkephalin-Lys-Lys-Glu-Glu-Glu-Lys-OH);

H-Tyr-Gly-Gly-Phe-Leu-Lys-Glu-Glu-Glu-Glu-Lys--OH (Leu-enkephalin-Lys-Glu-Glu-Glu-Glu-Lys-OH);

H-Tyr-Gly-Gly-Phe-Leu-Lys-Glu-Glu-Glu-Glu-Lys--OH (Leu-enkephalin-(Lys-Glu)$_3$;

H-Tyr-Gly-Gly-Phe-Leu-(Dpr)$_6$-OH (Leu-enkephalin-(Dpr)$_6$-OH);

H-Lys$_6$-Tyr-Gly-Gly-Phe-Leu-OH (H-Lys$_6$-Leu-enkephalin);

H-Tyr-Gly-Gly-Phe-Leu- Lys$_6$-OH (H-Leu-enkephalin-Lys$_6$);

H-Lys$_6$-Tyr-Gly-Gly-Phe-Leu-Lys$_6$-OH (H-Lys$_6$-Leu-enkephalin-Lys$_6$-OH);

Glu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-(Lys)$_6$-OH (GnRH-Lys$_6$-OH);

Glu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-(Lys-Glu)$_3$-OH (GnRH-(Lys-Glu)$_3$-OH); and

H-Ser-Val-Ser-Glu-Ile-Gln-Leu-Met-His-Asn-Leu-Gly-Lys-His-Leu-Asn-Ser-Met-Glu-Arg-Val-Glu-Trp-Leu-Arg-Lys-Lys-Leu-Gln-Asp-Val-His-Asn-Phe-(Lys-Glu)$_3$-OH (PTH 1-34 human-(Lys-Glu)$_3$-OH).

24. A method for the preparation of a pharmacologically active peptide conjugate (X-Z) as defined in claim 2, comprising the steps of:

a) coupling an N-α-protected amino acid in the carboxyl activated form or an N-α-protected dipeptide in the C-terminal activated form to an immobilised peptide sequence H-Z-SSM, thereby forming an immobilised N-α-protected peptide fragment,

b) removing the N-α-protecting group, thereby forming an immobilised peptide fragment having an unprotected N-terminal end,

c) coupling an additional N-α-protected amino acid in the carboxyl activated form, or an additional N-α-protected dipeptide in the C-terminal activated form to the N-terminal end of the immobilised peptide fragment, and repeating the removal/coupling step procedure in step b) and c) until the desired peptide sequence X is obtained, and then

d) cleaving off the peptide conjugate from the solid support material.

25. A method for the preparation of a pharmacologically active peptide conjugate (Z-X) as defined in claim 3, comprising the steps of:

a) coupling an N-α-protected amino acid, or an N-α-protected dipeptide to a solid support material (SSM), thereby forming an immobilised N-α-protected amino acid,

b) removing the N-α-protecting group, thereby forming an immobilised amino acid or peptide fragment having an unprotected N-terminal end,

c) coupling an additional N-α-protected amino acid in the carboxyl activated form, or an additional N-α-protected dipeptide in the C-terminal activated form to the N-terminal end of the immobilised amino acid or peptide fragment, and repeating the removal/coupling step procedure in step b) and c) until the desired peptide sequence X is obtained,

d) coupling an additional N-α-protected amino acid in the carboxyl activated form, or an additional N-α-protected dipeptide in the C-terminal activated form to the N-terminal end of the immobilised peptide fragment, and repeating the removal/coupling step procedure in step b) and d) until the desired peptide sequence Z is obtained, and then

e) cleaving off the peptide conjugate from the solid support material.

26. A method for the preparation of a pharmacologically active peptide conjugate (Z-X-Z) as defined in claim 4, comprising the steps of:

a) coupling an N-α-protected amino acid in the carboxyl activated form, or an N-α-protected dipeptide in the C-terminal activated form to an immobilised peptide sequence H-Z-SSM, thereby forming an immobilised N-α-protected peptide fragment,

b) removing the N-α-protecting group, thereby forming an immobilised peptide fragment having an unprotected N-terminal end,

c) coupling an additional N-α-protected amino acid in the carboxyl activated form, or an additional N-α-protected dipeptide in the C-terminal activated form to the N-terminal end of the immobilised peptide fragment, and repeating the removal/coupling step procedure in step b) and c) until the desired peptide sequence X is obtained, and then

d) coupling an additional N-α-protected amino acid in the carboxyl activated form, or an additional N-α-protected dipeptide in the C-terminal activated form to the N-terminal end of the immobilised peptide fragment, and repeating the removal/coupling step procedure in step b) and d) until the desired peptide sequence Z is obtained, and then

e) cleaving off the peptide conjugate from the solid support material.

27. A method for producing the peptide conjugate of claim 1, comprising
a) introducing a nucleic acid sequence encoding said conjugate into a host cell;
b) culturing said host cell and
c) isolating said conjugate from the culture.

28. A method for producing the peptide conjugate of claim 1, comprising
a) culturing a recombinant host cell comprising a nucleic acid sequence encoding said conjugate under conditions permitting the production of said conjugate; and
b) isolating said conjugate from the culture.

29. The method according to claim 28 or claim 29, wherein the nucleic acid sequence encoding said conjugate is contained within a nucleic acid construct or a vector.

30. A composition comprising a pharmacologically active peptide conjugate as defined in any of the claims 1-24, and a pharmaceutical acceptable carrier.

31. A composition comprising
H-Trp-Ala-Gly-Gly-Asp-Ala-Ser-Gly-Glu-(Lys-Glu)$_3$-OH,
H-Trp-Ala-Gly-Gly-Asp-Ala-Ser-Gly-Gln-(Glu)$_6$-OH,
H-Tyr-Gly-Gly-Phe-Leu-(Glu)$_6$-OH or
H-Tyr-Gly-Gly-Phe-Leu-(Lys)$_6$-OH, and a pharmaceutical acceptable carrier.

32. Use of a pharmacologically active peptide conjugate as defined in any of claims 1-23 for the manufacture of a pharmaceutical composition.

33 Use of a pharmacologically active peptide conjugate selected from the group consisting of

H-Trp-Ala-Gly-Gly-Asp-Ala-Ser-Gly-Glu-(Lys-Glu)$_3$-OH,
H-Trp-Ala-Gly-Gly-Asp-Ala-Ser-Gly-Glu-(Glu)$_6$-OH,
H-Tyr-Gly-Gly-Phe-Leu-(Glu)$_6$-OH and
H-Tyr-Gly-Gly-Phe-Leu-(Lys)$_6$-OH,
for the manufacture of a pharmaceutical composition.

34. Use of H-Trp-Ala-Gly-Gly-Asp-Ala-Ser-Gly-Glu-(Lys-Glu)$_3$-OH or H-Trp-Ala-Gly-Gly-Asp-Ala-Ser-Gly-Glu-(Glu)$_6$-OH for the manufacture of a pharmaceutical composition for the treatment of sleep disorders.

35. Use of H-Tyr-Gly-Gly-Phe-Leu-(Glu)$_6$-OH or H-Tyr-Gly-Gly-Phe-Leu (Lys)$_6$ OH for the manufacture of a pharmaceutical composition for the treatment of pain.

36. Use of a peptide conjugate according to any one of claims 1-23, wherein said pharmacologically active peptide X is enkephalin for the manufacture of a pharmaceutical composition for inhibiting neurons from transmitting pain impulses.

37. Use of a peptide conjugate according to any one of claims 1-23, wherein said pharmacologically active peptide X is enkephalin for the manufacture of a pharmaceutical composition for use in treatment of pain.

38. Use of a peptide conjugate according to any one of claims 1-23, wherein said pharmacologically active peptide X is growth hormone releasing hormone or growth hormone releasing peptide for the manufacture of a pharmaceutical composition for use in stimulating the release of growth hormone.

39. Use of a peptide conjugate according to any one of claims 1-23, wherein said pharmacologically active peptide X is EMP-1 for the manufacture of a pharmaceutical composition for increasing hemoglobin levels.

40. Use of a peptide conjugate according to any one of claims 1-23, wherein said pharmacologically active peptide X is EMP-1 for the manufacture of a pharmaceutical composition for use in treating anemia by increasing hemoglobin levels.

41. Use of a peptide conjugate according to any one of claims 1-23, wherein said pharmacologically active peptide X is parathyroid hormone for the manufacture of a pharmaceutical composition for use in preventing or treating bone loss by altering the balance between ostoclastic and osteoblast activity.

42. Use of a peptide conjugate according to any one of claims 1-23, wherein said pharmacologically active peptide X is parathyroid hormone for the manufacture of a pharmaceutical composition for use in preventing or treating osteoporosis.

43. Use of a peptide conjugate according to any one of claims 1-23, wherein said pharmacologically active peptide X is glucagon-like peptide-1 for the manufacture of a pharmaceutical composition for reducing blood glucose levels.

44. Use of a peptide conjugate according to any one of claims 1-23, wherein said pharmacologically active peptide X is glucagon-like peptide-1 for the manufacture of a pharmaceutical composition for use in treatment of diabetes.

45. Use of a peptide conjugate according to any one of claims 1-23, wherein said pharmacologically active peptide X is gonadotropin releasing hormone, for the manufacture of a pharmaceutical composition for regulating the production of sex hormones.

46. Use of a peptide conjugate according to any one of claims 1-23, wherein said pharmacologically active peptide X is gonadotropin releasing hormone for the manufacture of a pharmaceutical composition for use in regulating the level of sex homones.

47. Use of a peptide conjugate according to any one of claims 1-23, wherein said pharmacologically active peptide X is delta-sleep inducing peptide for the manufacture of a pharmaceutical composition for use in treating a sleep disorder.

48. Use of a peptide conjugate according to any one of claims 1-23, wherein said pharmacologically active peptide X is antiarrythmic peptide for the manufacture of a pharmaceutical composition.

49. Use of a stabilising peptide sequence (Z) as defined in claim 1 for the preparation of a pharmacologically active peptide conjugate as defined in any of claims 1-23 or a salt thereof.